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EXAMINER	
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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/646,932	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,30,31 and 37-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,30,31 and 37-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group 6, claims 14, 30-31 in the response of 11/19/07 and 04/21/08 is acknowledged.

Applicant adds new claims 37-49.

Accordingly, Group 6, claims 14, 30-31, 37-49 are examined in the instant application.

Objection

Claims 14, 30-31, 42-49 are objected to for the use of the abbreviated language "PBR".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 30-31, 37-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 14, 30-31 are indefinite for the use of the relative language "aggressive". Aggressive cancer is not necessarily metastatic cancer, since any stage of a cancer is aggressive when compared to non-cancerous tissue.

2. Claims 37-41, 43-47, 49 are indefinite, because there is no reference point for codon 147 or codon 162 cited in claims 37, 38, 46-47, in view of the absence of the recitation of

a sequence identification number in the claims, and in view that variant PBRs do not necessarily have the same structure and size as that of the wild type PBR.

3. Claim 38 is indefinite, because it is not clear how a duplex DNA molecule "corresponds" to the RNA.

4. Claims 42-49 are indefinite for the use of the language "wild type". It is not clear what constitutes a wild type PBR. This rejection could be obviated, by amending the claims, for example, to add a sequence identification number of the wild type PBR.

Claim Rejections - 35 USC § 112, First Paragraph, Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 30-31, 37-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:1) a method for diagnosis of metastatic breast cancer, by detecting an increase in the level of the wild-type PBR mRNA known in the art (e.g., Miettinen et al, 1995, Cancer Res, 55: 2691-2695, IDS of 11/19/07) in a breast cancer tissue as compared to a non-cancerous breast tissue, and 2) a method for detecting the presence of the PBR variant SEQ ID NO:1 or SEQ ID NO:2 in a breast cancer cell line, does not reasonably provide enablement for: 1) a method for diagnosing an aggressive tumor phenotype in a tumor tissue sample, by detecting an increase in the level of PBR RNA, 2) a method for detecting the presence of a variant PBR, SEQ ID NO:1, or SEQ ID NO: 2 in a physiological sample, which sample encompasses a tumor biopsy, a breast or colon cancer biopsy, and 3) a method for

detecting the relative level of variant PBR in a sample as compared to that of wild-type PBR, which sample is not necessarily a breast cancer cell line. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that the level of wild type PBR mRNA is increased in aggressive, metastatic human breast cancer biopsy as compared to non-cancerous breast tissue (Examples 5- 6 on pages 43-45, and figures 9-10). The specification discloses that the partial cDNA sequence of variant PBR SEQ ID NO:1 or SEQ ID NO:2 is detected in two breast cancer cell lines (p.15-16).

Other than the breast cancer cell lines, the specification, however, does not have any data or objective evidence showing the presence of or an increase in the level of the partial cDNA sequence of variant PBR SEQ ID NO:1 or SEQ ID NO:2 in any other type of sample, such as a sample obtained directly from a patient, e.g. a tissue cancer sample.

1. Claims 14, 30-31 are rejected under 112, first paragraph, for lack of enablement for a method for **diagnosing an aggressive tumor phenotype** in **a tumor tissue sample** by detecting an increase in the level of **PBR RNA.**

i) Claims 14, 30-31 would be **non-specific**, because: 1) the hybridization conditions are not recited, and would encompass any hybridization conditions, wherein under low hybridization conditions, the claimed oligonucleotides or primers would recognize unrelated sequences besides PBR RNA, and 2) and the cited oligonucleotide probes or primers are not necessarily specific for PBR RNA. Therefore, one cannot predict whether an increase in the level of PBR RNA would be detected.

ii) Moreover, claims 14, 30-31 encompass a method for diagnosis of aggressive tumor phenotype, by detecting an increased level of **variant PBR** RNA, because PBR without being accompanied by a sequence identification number encompasses variant PBR.

One cannot predict that a variant PBR RNA, such as variant PBR with a substitution at codon 147 or codon 162, or the variant PBR of SEQ ID NO:1 or SEQ ID NO:2 would be detected in any tumor cells other than breast cancer cell lines, such as a tumor biopsy, a breast tumor biopsy or a colon cancer biopsy, due to the well known **cell culture artifact**. SEQ ID NO:1 or SEQ ID NO:2 is only shown to be detected in two breast cancer cell lines. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al, 1993 (Leukemia and Lymphoma, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even

for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al, 1984 (Immunol Ser, 23:181-207) teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu, 1973 (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian, J et al, 2004 (Physiol Genomics, 17: 170-182), teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke D L et al, 2003 (Cancer Genetics and Cytogenetics 241: 137-141), teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments). Zaslav A L et al, 2002 (Amer J Medical Genetics 107: 174-176), teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p.

175, first column, paragraph under Discussion).). Kunkel, P, et al, 2001 (Neuro-oncology 3(2): 82-88), teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract). The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays For the reasons set forth above, one cannot predict that a variant PBR RNA, such as variant PBR RNA with a substitution at codon 147 or codon 162, or the variant PBR of SEQ ID NO:1 or SEQ ID NO:2 would be detected in any tumor cell sample, such as a tumor biopsy, a breast tumor biopsy or a colon cancer biopsy.

iii) Further, claims 14, 30-31 encompass a method for diagnosis of an aggressive tumor phenotype in **any metastatic cancer**, by detecting an increase in the PBR mRNA level in said cancer as compared to normal tissue sample.

Although the level of wild type PBR RNA is known to be increased in various cancers (see Venturini et al, 1998, Life Sciences, 63(14): 1269-1280), one cannot predict that **aggressive, metastatic** cancers, other than metastatic breast cancer, and high grade brain cancer (see Miettinen et al, 1995, Cancer Res, 55: 2691-2695, IDS of 11/19/07), would have an increase in the level of PBR mRNA as compared to the corresponding non-cancerous tissue, because because expression of a sequence could be lost during the progression toward metastasis. For example, Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the

chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis. Similarly, Dong et al, 2000, Cancer Research, 60: 3880-3883, teach that deletion of a region in the chromosome 13q21 is associated with aggressive prostate cancer, as compared to less aggressive prostate cancer, such as primary prostate cancers that are not yet differentiated (abstract, and figure 1 on page 3882). Zhau, HE, 1994, J Cell Biochem, Suppl 19: 208-216, teach expression of various biomarkers associated with prostate cancer progression. Zhau et al teach that in prostate cancer, PC-3N35 subclones which are cloned from primary and metastatic sites (lymph node, kidney and bone), show difference in the levels of protein expression of various markers, such as c-erbB, vimentin, ICAM-1, cytokeratin, collagen IV between the parental PC-3N35 clone and its metastatic subclones (p.209 and table 1) and that the subline derived from the metastatic site lymph node has a 12p:17q translocation, whereas the bone-derived subline contains an isochromosome 7q (p.211, first column, first paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that the level of PBR mRNA is increased in aggressive, metastatic cancers other than metastatic breast and brain cancer, as compared to corresponding non-cancerous tissue.

iv) Further, since it is not clear what constitutes a **normal cell or tissue**, which is not necessarily a non-cancerous tissue corresponding to the tested cancer tissue, and the level of the claimed PBR in which normal cell or tissue is not predictable, one would not know how to perform the claimed method.

v) In addition, a **tumor** encompasses any enlargement or abnormal growth, which is not necessarily cancerous, for example, cystic of the pancreas, splenic tumor or enlargement of the

spleen, etc… (Stedman's medical dictionary, 25th ed, 1990, p.1652-1653). One cannot predict that one can successfully diagnose aggressive cancer, wherein the cells to be assessed are tumor cells, which are not necessarily cancerous, and are unrelated to cancer, and thus having different etiology and characteristics, and would not predictably express the same level of PBR mRNA as the aggressive breast cancer tissue.

vi) Moreover, claims 14, 30-31 encompass a method for detecting **any variant PBR RNA**. Other than the PBR variant of SEQ ID NO:1 and SEQ ID NO:2, one cannot predict that there exist other variant PBR, because mutation is an unpredictable event.

2. Claims 37-41, 43-45, 49 are rejected under 112, first paragraph, for lack of enablement for a method for detecting the presence of **a variant PBR with a substitution at codon 147 or codon 162, or the variant PBR of SEQ ID NO:1 or SEQ ID NO:2, in a physiological sample, such as a tumor biopsy, a breast tumor biopsy or a colon cancer biopsy.**

i) One cannot predict that a variant PBR with a substitution at codon 147 or codon 162, or the variant PBR of SEQ ID NO:1 or SEQ ID NO:2 would be detected in **any physiological sample** other than breast cancer cell lines, such as a tumor biopsy, a breast tumor biopsy or a colon cancer biopsy, due to the well known **cell culture artifact**, supra. SEQ ID NO:1 or SEQ ID NO:2 is only shown to be detected in breast cancer cell lines. Characteristics of cultured cell lines, however, generally differ significantly from the characteristics of a primary tumor.

ii) Further, since there is **no point of reference** for codon 147 or codon 162 in the claimed PBR variant, one would not know how to make the claimed variant PBR nucleic acid for use in the claimed method.

iii) In addition, the specification fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses detecting a variant PBR **gene**. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and one cannot predict the structure of the claimed variant PBR gene.

iv) In addition, a **tumor** encompasses any enlargement or abnormal growth, which is not necessarily cancerous, for example, cystic of the pancreas, splenic tumor or enlargement of the spleen, etc… (Stedman's medical dictionary, 25th ed, 1990, p.1652-1653, supra). Even if the claimed PBR variant were present or overexpressed in aggressive breast cancer tissue, one cannot predict that one can successfully detect the presence of the claimed PBR variant in a tumor, wherein the cells to be assessed are tumor cells, which are not necessarily cancerous, and are unrelated to cancer, and thus have different etiology and characteristics, and would not predictably express the variant PBR mRNA as the aggressive breast cancer tissue.

3. Claims 42-49 are rejected under 112, first paragraph for lack of enablement for **a method for detecting the relative level of variant PBR RNA in a sample as compared to the level of wild-type PBR RNA.**

i) The claimed method would be non-specific, because hybridizing as cited in claim 42 encompasses **hybridizing under any conditions**. Under low stringency hybridization conditions, any non-related sequence would hybridize to the claimed probe.

ii) In addition, one cannot predict that **any sample** could be used for the claimed method, because one cannot predict that the claimed variant PBR would be expressed in any sample other than breast cancer cell lines, due to **cell culture artifact**, supra, and because expression or the presence of a particular nucleic acid in a particular tissue or a cancer is not predictable.

iii) Further, even if the claimed variant PBR were present in a tested sample, one cannot predict that there is a **difference in the level** of the claimed variant PBR mRNA and that of the wild type PBR mRNA in said sample, because the expression level of a sequence, including a variant in a specific tissue or in a cancer is not predictable. Since one cannot predict that there is a difference in the level of the claimed variant PBR mRNA and that of the wild type PBR mRNA in a sample, one would not know how to use the claimed method.

iv) Further, since there is **no point of reference** for codon 147 or codon 162 in the claimed PBR variant, as claimed in claims 46, 47, one would not know how to make the claimed variant PBR nucleic acid for use in the claimed method.

v) Moreover, claims 42-45, 48 encompass a method for detecting **any variant PBR RNA**. Other than the PBR variant of SEQ ID NO:1 and SEQ ID NO:2, one cannot predict that there exist other variant PBR, because mutation is an unpredictable event.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 37-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Hardwick et al, February 15, 1999, Cancer Res, 59: 831-842, IDS of 11/19/07, and as evidenced by Sambrook et al, 1989, Molecular Cloning, A laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p.14.1-14.4.

Claims 37-38 are as follows:

37. (Previously Presented) A method to detect the presence of a variant peripheral-type benzodiazepine receptor (PBR) gene in a physiological sample, comprising: determining whether RNA obtained from a physiological sample encodes a variant PBR with a substitution at codon 147 or at codon 162.

38. (Previously Presented) The method of claim 37 comprising (i) extracting RNA from the sample; (ii) subjecting the RNA to conditions that result in a duplex DNA molecule corresponding to the RNA; (iii) amplifying at least a portion of the duplex DNA to achieve linear production of amplified DNA; (iv) determining whether the amplified DNA encodes a variant PBR with a substitution at codon 147 or at codon 162.

Hardwick et al teach detection of variant PBR mRNA in two human breast cancer cell lines (abstract). Hardwick et al teach that the partial variant cDNA sequences are prepared using PCR for sequencing, and that when aligned and compared with the wild type PBR, the variant PBR has substitution at Ala 147 to Thr and His 162 to Arg (p.832, second column, item under "Partial cDNA Sequencing", and figure 6 on page 840).

It is well known in the art that PCR involves formation of duplex DNA, and amplication of the DNA by polymerase chain reaction, as evidenced by Sambrook et al (Sambrook et al, p.14.1-14.4).

2. Claims 14, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Miettinen et al, 1995, Cancer Res, 55: 2691-2695, IDS of 11/19/07.

Claims 14, 31 are as follows:

14. (Original) A method for diagnosing an aggressive tumor phenotype comprising:

(i) contacting a tumor tissue sample with oligonucleotides which recognize PBR RNA;

(ii) detecting the presence or absence of a duplex formed between PBR RNA in said sample and oligonucleotides specific therefor;

(iii) and comparing it to the amount of duplex formed in a normal tissue sample, wherein an increase in duplex in the suspected tissue over normal indicates the presence of an aggressive tumor phenotype.

31. (Original) A method for determining the aggressive phenotype of a tumor cell detecting PBR RNA in said cell and comparing the level of PBR RNA to the level of PBR RNA from a normal cell wherein an increase over normal in PBR RNA in the tumor cell indicates an aggressive tumor phenotype.

This rejection only applies to PBR RNA interpreted as **wild type PBR RNA**.

Miettinen et al teach that the level of PBR mRNA is increased and correlates with brain cancer grade, with moderate amount of PBR in grade II and III astrocytoma, and strongest in grade IV glioblastoma, as compared to non-detectable PBR mRNA in normal cortex and low-grade astrocytoma (abstract, p.2693, item under "Results", p.2694). Miettinen et al teach that PBR mRNA is detected using oligonucleotide specific for PBR and in situ hybridization (p.2693, first column, item under "In situ hybridization").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miettinen et al, 1995, Cancer Res, 55: 2691-2695, supra, in view of Sambrook et al, 1989, Molecular Cloning, A laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p.14.1-14.4.

Claim 30. (Original) A method for detecting the level of PBR in cells using the polymerase chain reaction said method comprising:

(i) extracting RNA from a sample;

(ii) reverse transcribing said RNA into cDNA

(ii) contacting said cDNA with

(a) at least four nucleotide triphosphates,

(b) a primer that hybridizes to PBR cDNA, and

(c) an enzyme with polynucleotide synthetic activity, under conditions suitable for the hybridization and extension of said first primer by said enzyme, whereby a first DNA product is synthesized with said DNA as a template therefor, such that a duplex molecule is formed;

(iii) denaturing said duplex to release said first DNA product from said DNA;

(iv) contacting said first DNA product with a reaction mixture comprising:

(a) at least four nucleotide triphosphates,

(b) a second primer that hybridizes to said first DNA, and

(c) an enzyme with polynucleotide synthetic activity, under conditions suitable for the hybridization and extension of said second primer by said enzyme, whereby a second DNA product is synthesized with said first DNA as a template therefor, such that a duplex molecule is formed;

(v) denaturing said second DNA product from said first DNA product; (vi) repeating steps iii-vi for a sufficient number of times to achieve linear production of said first and second DNA products;

(vii) fractionating said first and second DNA products generated from said PBR cDNA; and

(viii) comparing the level of PBR cDNA with the level of PBR cDNA from a normal cell; wherein, an increase in PBR level over normal cells indicates an aggressive tumor phenotype.

This rejection only applies to PBR RNA interpreted as **wild type PBR RNA**.

The teaching of Miettinen et al has been set forth above.

Miettinen et al do not teach the use of PCR for detecting the PBR mRNA.

Sambrook et al teach how to detect nucleic acid, using PCR, in which two primers are used for extension and amplification of the DNA template (p.14.1-14.4).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to replace in situ hybridization taught by Miettinen et al with the PCR method taught by Sambrook et al to detect PBR mRNA in a brain cancer, as taught by Miettinen et al, to expand the versatility of the detection methods.

2. Claims 14, 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miettinen et al, 1995, Cancer Res, 55: 2691-2695, supra, in view of Venturini et al, 1998, Life Sciences, 63(14): 1269-1280, Hardwick et al, February 15, 1999, Cancer Res, 59: 831-842, supra, Tong et al, 1991, Regulatory peptides, 33: 263-273, and Sambrook et al, 1989, Molecular Cloning, A laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p.14.1-14.4.

Claims 14, 30-31 are as follows:

14. (Original) A method for diagnosing an aggressive tumor phenotype comprising:

(i) contacting a tumor tissue sample with oligonucleotides which recognize PBR RNA;

(ii) detecting the presence or absence of a duplex formed between PBR RNA in said sample and oligonucleotides specific therefor;

(iii) and comparing it to the amount of duplex formed in a normal tissue sample, wherein an increase in duplex in the suspected tissue over normal indicates the presence of an aggressive tumor phenotype.

30. (Original) A method for detecting the level of PBR in cells using the polymerase chain reaction said method comprising:

(i) extracting RNA from a sample;

(ii) reverse transcribing said RNA into cDNA

(ii) contacting said cDNA with

(a) at least four nucleotide triphosphates,

(b) a primer that hybridizes to PBR cDNA, and

(c) an enzyme with polynucleotide synthetic activity, under conditions suitable for the hybridization and extension of said first primer by said enzyme, whereby a first DNA product is synthesized with said DNA as a template therefor, such that a duplex molecule is formed;

(iii) denaturing said duplex to release said first DNA product from said DNA;

(iv) contacting said first DNA product with a reaction mixture comprising:

(a) at least four nucleotide triphosphates,

(b) a second primer that hybridizes to said first DNA, and

(c) an enzyme with polynucleotide synthetic activity, under conditions suitable for the hybridization and extension of said second primer by said enzyme, whereby a second DNA

product is synthesized with said first DNA as a template therefor, such that a duplex molecule is formed;

(v) denaturing said second DNA product from said first DNA product; (vi) repeating steps iii-vi for a sufficient number of times to achieve linear production of said first and second DNA products;

(vii) fractionating said first and second DNA products generated from said PBR cDNA; and

(viii) comparing the level of PBR cDNA with the level of PBR cDNA from a normal cell; wherein, an increase in PBR level over normal cells indicates an aggressive tumor phenotype.

31. (Original) A method for determining the aggressive phenotype of a tumor cell detecting PBR RNA in said cell and comparing the level of PBR RNA to the level of PBR RNA from a normal cell wherein an increase over normal in PBR RNA in the tumor cell indicates an aggressive tumor phenotype.

This rejection only applies to PBR RNA interpreted as **wild type PBR RNA**.

Further, since aggressive, as claimed in claims 14, 30-31, is a relative term, one would reasonably interpret that **any cancer would be aggressive**, as compared to non-cancerous tissue control.

The teaching of Miettinen et al has been set forth above.

Miettinen et al do not teach the use of PCR for detecting the PBR mRNA. Miettinen et al do not teach detection of PBR RNA in cancer such as hepatoma, colon, ovarian or breast cancer.

Venturini et al teach that PBR protein is up-regulated in hepatoma, using a ligand specific for PBR (abstract, p.1273, 1275). Venturini et al teach that it is known in the art that PBR also increases in concentration in brain, ovarian, and colon cancer (abstract, p.1273, 1275-1276).

Hardwick et al teach the level of PBR protein is increased in aggressive, metastatic breast cancer biopsy as compared to normal breast tissue (p.834, second column).

Tong et al teach that level of PBR protein is higher in DMBA-induced mammary tumors in rat as compared to non-cancerous, resting or lactating mammary glands (abtract, p.271, second paragraph).

Sambrook et al teach how to detect nucleic acid, using PCR, in which two primers are used for extension and amplification of the DNA template (p.14.1-14.4).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to replace in situ hybridization taught by Miettinen et al with the PCR method taught by Sambrook et al to detect PBR mRNA in a brain cancer, as taught by Miettinen et al, to expand the versatility of the detection methods.

Moreover, it would have been obvious to expand the in situ hybridization or PCR detection method taught by Miettinen et al and Sambrook et al to other cancers, such as hepatoma, ovarian, colon or breast cancer, as taught by Venturini et al, Hardwick et al, and Tong et al, because these cancers have an increase level of PBR protein as compared to non-cancerous corresponding tissue, and because the RNA level would reflect its encoded protein level.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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